situation in *Wands* is highly analogous to that at hand. In *Wands,* the Federal Circuit held that claims to generic monoclonal antibodies were enabled by a specification that taught the entire procedure of making monoclonal antibodies. Moreover, in view of the high level of skill in the art and routine nature of each step of the antibody-making procedure, the court held that the amount of experimentation required to make other monoclonals was extensive, but not undue.

Like the applicant in *Wands*, Applicant has established that the specification at issue teaches each and every step of the claimed methods. The pending claims are not, as asserted by the Office, directed to any and all bispecific antibodies. Instead, the claims are limited to methods of inducing antibodies to a cancer antigen using bispecific antibodies having the recited binding specificity. Accordingly, Applicant's specification need only teach one of skill in the art how to practice methods of inducing antibodies using a bispecific antibody in order to satisfy the enablement requirement of section 112. The specification clearly satisfies this requirement. Indeed, how to make bispecific antibodies, how to administer these antibodies and how to determine a patient's humoral response to one of the antigens recognized by the bispecific antibodies are all fully described in the specification. (*See, e.g.*, pages 9, line 12-28 describing generation of bispecific antibodies, pages 17-20 describing cancer antigens, and pages 24-29 describing testing of subjects for antibody production). Working examples, detailing each claimed step, are set forth. Following the examples and guidance set forth by Applicant, a skilled artisan could readily practice the claimed methods. Thus, for the reasons previously of record and those reiterated herein, Applicant again submits that the specification fully enables the claimed methods.

Applicant also traverses the Examiner's assertion that various references establish that the claimed invention is unpredictable. (Rudikoff, Adair and Panka, cited on page 5 of the Final Office Action). In citing these references, the Examiner asserts, "the specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claimed." (See, page 5, Final Office Action). The Examiner's position appears to be that, due to recognized variability of CDRs, the claimed methods are unpredictable.

As a threshold matter, Applicant notes that enablement and predictability are determined as of the time of filing. Here, Rudikoff was published 12 years prior to Applicant's filing date; Adair 3 years prior; and Panka 6 years prior. Thus, none of these references are indicative of the state of the art in December 1994, the time this application was filed. Indeed, patents directed to production of bispecific antibodies have routinely issued by the Office. (*See, e.g.,* U.S. Patent No. 4,474,893 cited on page 9, line 20 of the specification). Thus, contrary to the Examiner's assertion, at the time the pending application was filed, many of the problems associated with production of antibodies had been solved and these solutions were publicly available.

Even assuming, for the sake of argument only, that Rudikoff, Adair and/or Panka were representative of the state of the art as of Applicant's filing date, these references do not in any way establish unpredictability of methods involving the claimed bispecific antibodies to produce antibodies. In fact, none of these references address using bispecific antibodies at all, let alone using the particularly claimed bispecific antibodies to induce production of an antibody response. These references are a far cry away from establishing that the claimed methods are not enabled by Applicant's specification.

Moreover, the existence of potentially inoperative or ineffective embodiments does not mean that the enablement requirement is not satisfied. Indeed, if any uses of multiple uses disclosed in the specification are enabled, the application is enabling. See, Training Manual on Enablement, page 21. As noted in Dr. Wong's attached Rule 132 Declaration:

> 8. Furthermore, the specification provides working examples and additional significant direction for evaluating whether a FcγRIII-cancer antigen binding bispecific antibody could be used to elicit an antibody response to the cancer antigen. Those of us working in the field of bispecific antibodies are well versed in administration of antibodies and in the various tests for determining whether antibodies are elicited, for example using assays described on pages 24-29 of the specification. Examples present in the specification demonstrate such assays. (See, Examples 2 and 3). Furthermore, since preparing bispecific antibodies in December of 1994 was well within the purview of a skilled worker, even if a particular bispecific antibody were inoperable for some reason (*e.g.*, it did not elicit antibodies against the cancer antigen), the skilled worker would have readily used the molecule as a starting point in order to design bispecific antibodies with the desired characteristics.

For the reasons detailed above and previously made of record, Applicant's specification describes and demonstrates that the claimed methods are operative and, accordingly, the various references cited by the Office are not relevant to the claimed invention and certainly do not establish unpredictability of the claimed invention.

Despite the Office's failure to establish a *prima facie* case of non-enablement, Applicant has submitted still further evidence establishing that the specification fully enables the pending claims throughout their scope. The Office must consider evidence provided by the applicant that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *See, e.g.*, PTO Training Manuals on Enablement, page 42; MPEP 716.09; *In re Brandstadter,* 179 USPQ 286 (CCPA 1973); *In re Ambruster,* 185 USPQ 152 (CCPA 1975); and *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). The evidence provided by the applicant

need not be conclusive but merely convincing to one skilled in the art. PTO Training Manual on Enablement, page 42.

In this regard, Dr. Justin Wong's Rule 132 Declaration, copy attached hereto as Appendix A, supports Applicant's position regarding enablement in all respects. In this declaration, Dr. Wong establishes that practicing the claimed methods would not require undue experimentation in view of the guidance of the specification and general knowledge available at the time of filing:

> 7. In December 1994, the quantity of experimentation required to make bispecific antibodies that recognized FcγRIII and a cancer antigen was quite low. At the time of filing and as described in the specification, FcγRIII was a well-characterized isoform of the CD16 cell surface receptor. (*See,* for example, page 10, lines 6-16). One working in this field could have readily selected suitable cancer antigens, for example as described in detail on pages 17-20. Also well known at the time of filing were techniques of producing bispecific antibodies and these standard procedures are described throughout the specification as filed, for example, on page 9, line 12-28 (including the references cited therein). Based on these extensive teachings regarding each of the antigens recognized by the claimed bispecific antibody and, additionally, the extensive teachings regarding production of bispecific antibodies, it is evident that a skilled worker would have easily produced bispecific antibodies which bound both FcγRIII and a cancer antigen. Thus, it is clear from the specification that 2B1 is merely one example of a hybrid hybridoma capable of producing bispecific monoclonal antibody. Therefore, it is my opinion that it would have required only routine experimentation for the skilled worker to make a bispecific antibody that recognized FcγRIII and a cancer antigen, as recited in the pending claims.

Based on the teachings of the specification and the state of the art at the time of filing, Dr. Wong confirms that it would have required little or no experimentation for one skilled in the art to identify suitable bispecific antibodies and evaluate these antibodies for their ability to generate antibodies against a cancer antigen. (See, Wong Declaration, paragraphs 7-10).

Thus, there is ample evidence of record in the present case demonstrating that the specification as filed fully enables the pending claims. When the factors in *Wands* are weighed, it would not require undue experimentation to practice the claimed invention, given the guidance found in the specification and state of the art. The claimed invention is, therefore, enabled. Therefore, the rejections under section 112, first paragraph are improper and Applicant respectfully requests these rejections be withdrawn.

Rejections Under 35 U.S.C.§ 103(a)

Claims 1-3, 8, and 15 stand rejected as allegedly unpatentable over Hsieh-Ma et al. (Cancer Research, 1992) or Weiner et al. (Cancer Research, 1993) or Ring et al. (Breast

Epithelial Antigens, 1991) in view of Fanger et al. (Critical Reviews in Immunology, 1992) or Snider et al. (J. Exp. Med. 171:1957-1963, 1990). Collectively, Hseih-Ma, Weiner and Ring are referred to as the "primary references." In addition, claims 1-3, 5-8, and 15 also stand rejected as allegedly obvious over the primary references in view of Fanger or Snider and in further view of U.S. Patent No. 6,054,561.

In support of the rejections, the Office Action maintains that the primary references teach all the limitations of the claims except for antibody production to the second antigen. (Office Action, paragraph 6, page 6). Fanger and Snider are cited for alleging teaching that bispecific antibodies targeted to the APC cell antigens induce production of antibodies to the second antigen. (Office Action, paragraph 6, page 6). Further, in rejecting Applicant's previous arguments the Office Action states:

> the burden of proof is upon Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed antibodies with the antibody and the 2B1 antibody of the prior art.

Because the Office has not applied the proper legal standard to determining obviousness, Applicant traverses the rejections and supporting remarks.

As previously noted, a *prima facie* case of obviousness cannot be maintained where the references fail to teach or suggest all the limitations of the claims. MPEP 2143.03. Further, contrary to the Office's assertion, obviousness **cannot** be predicated on what is unknown. *In re Shetty, supra* quoting *In re Sporman,* 150 USPQ 449 (CCPA 1966). In addition, a functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used. (M.P.E.P. 2173.05(g) Functional Limitations, Eighth Edition). There is nothing inherently wrong with defining some part of an invention in functional terms and functional language does not, in and of itself, render a claim improper. *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971). Indeed, where the particular intended result (in this case production of antibodies to specified antigens) is a limitation of the pending claims it is entirely relevant to patentability.

Here, the pending claims expressly recite that the claimed methods must result in the production of antibodies directed against the cancer antigen and, hence, this limitation is relevant to patentability. It is unacceptable for the Office to ignore this limitation and assert that any art related to the making or using of bispecific antibodies is relevant, much less than it renders the particularly claimed invention unpatentable. Likewise, the Office cannot ignore the legal axiom that obviousness cannot be based on what was allegedly inherent. Thus, when the proper legal

standards of obviousness are applied, it is clear that the claimed methods, drawn to production of antibodies using bispecific antibodies, are in no way obvious over the cited references.

It is also legally and factually incorrect for the Office to assert "the burden of proof is upon Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed antibodies with the antibody and the 2B1 antibody of the prior art." (Final Office Action, page 6). In reality, the burden of proof is on the Office to establish a *prima facie* case of obviousness. MPEP 2143. Even assuming, for the sake of argument only, that a *prima facie* case of obviousness had been established, Applicant's burden would be to rebut obviousness of the claimed subject matter as a whole. In other words, in the pending case Applicant need not address 2B1 *per se* but, rather, what the combination of cited references suggests about the claimed methods, namely methods of inducing antibodies to a cancer antigen. For the reasons of record and reiterated herein, the cited references teach nothing regarding production of antibodies to cancer antigens using bispecific antibodies as claimed and, as such, do not render the claims unpatentable.

The factual underpinnings of the Examiner's rejections are also erroneous. As previously noted, although it is acknowledged that the primary references do not teach or suggest that bispecific antibodies would induce antibodies to cancer antigens, the secondary references (Fanger and Snider) are alleged to remedy this deficiency. (Final Office Action, paragraph 6). However, it is clear that Fanger and Snider teach **nothing** regarding antibody production. Fanger is directed entirely to use of bispecific antibodies in cellular immune responses, to localize toxins, to study the molecular specificity of particular receptor and/or as adjuvants. (See, Fanger, Abstract). Likewise, Snider teaches only that bispecific antibodies are useful as adjuvants. (See, Snider, Abstract). Finally, with regard to U.S. Patent No. 6,054,561, Applicant notes that this document is not available as a reference against the pending application because its earliest priority date is June 7, 1997, fully 3 years after the effective filing date of the pending application. There is, therefore, no combination of references that teaches all the limitations of the pending claims and no combination of references would reasonably lead one of skill in the art to the claimed methods.

In brief, there are absolutely no teachings in the cited references that provide the motivation to arrive the claimed methods. Indeed, all of the references are completely silent as to production of antibodies against the second antigen recognized by a bispecific antibody. Thus, there is no motivation to combine the references and, since obviousness cannot be predicated on inherency, a *prima facie* case of obviousness cannot be sustained. Accordingly, Applicant respectfully requests that the rejections under section 103 be withdrawn.

CONCLUSION

In view of the foregoing, Applicant submits that the claims are now in condition for allowance and requests early notification to that effect.

Please direct all further communications regarding this application to:

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Currently Pending Claims

1. (Amended) A method of inducing production of antibodies against a cancer antigen, comprising the step of administering a bispecific antibody to the patient, said bispecific antibody comprising a first binding site capable of recognizing and binding a first antigen wherein said first antigen is FcγRIII and further comprising a second binding site capable of recognizing and binding a second antigen, in an amount sufficient to induce production of antibodies to said second antigen in said patient, wherein said second antigen is a cancer antigen selected from the group consisting of c-erbB-2, HMW mucin, HMW mucin II, p-glycoprotein and an antigen recognized by a monoclonal antibody produced by any of the following hybridomas: ATCC Accession Nos HB 11830, HB 11769, HB 11768, HB 10798, HB 10802, HB 8490, HB 8485, HB 8691, HB 11052, HB 10812, HB 8486, HB 10789, HB 8488, HB 8662, HB 8697, HB 10785, HB 10796, HB 10793, HB 11752, HB 10795, HB 10801, HB 11751 and HB 10794 and further wherein said second binding site comprises a binding site derived from a monoclonal antibody produced by a hybridoma selected from the group consisting of: HB11830, 452F2 (HB 10811), 741F8 (HB 10807), 759E3 (HB 10808), 454C11 (HB 8484), 387H9 (HB 10802), 113F1 (HB 8490), 317G5 (HB 8485, HB 8691), 34F2 (HB 11052), 650E2 (HB 10812), 35E6 (HB 11769), 266B2 (HB 8486), 106A10 (HB 10789), 260F9 (HB 8488 and HB 8662), 33F8 (HB 8697), 9C6 (HB 10785), 35E10 (HB 10796), 140A7 (HB 10798), 36H3 (HB11768), 788G6 (HB 8692), 200F9 (HB 10791), 697B3 (HB 10806), 120H7 (HB 10790), 203E2 (HB 10799), 254H9 (HB 10792), 245E7 (HB 8489), 2G3 (HB 8491), 369F10 (HB 8682), 15D3 (HB 11342), 421E8 (HB 10793), 310B7 (HB 11752), 32A1 (HB 10795), 219F3 (HB 10801), 42E7 (HB 11751), and 388D4 (HB 10794).

2. The method according to claim 1, wherein said first binding site is a binding site derived from the monoclonal antibody produced from the 3G8 hybridoma.

3. The method according to claim 1, wherein said second antigen is present in the patient.

8. The method according to claim 1, wherein said bispecific antibody is produced by the hybrid hybridoma CRL 10197.

15. The method according to claim 1, wherein said second antigen is not present in the patient upon first administration of the bispecific antibody.